76. (Twice Amended) The method of claim 23, wherein said peptidyl PYY agonist enhances or recovers glucose responsiveness.

77. (Twice Amended) The method of claim 21, wherein said peptidyl PYY agonist enhances or recovers glucose responsiveness.

78. (Twice Amended) The method of claim 33, wherein said peptidyl PYY agonist enhances or recovers glucose responsiveness.

REMARKS

Claims 1-13 and 15-91 constitute the pending claims in the present application. Claims 87-91 have been added. The subject matter of these claims is fully supported by the specification as filed. Claims 1-12, 24-27, 34-38, 40, 41, 44, 47-49, and 52 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter. Applicants submit, however, that claims 25-27, 34-37, 52, and 53-86 are properly dependent on elected independent claims and should be considered together upon determining that such independent claims are allowable, pursuant to MPEP 809.02(c). Accordingly, all of these claims are presented above. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note with appreciation the entry of the amendments filed November 27, 2001, as indicated in the Advisory Action mailed December 17, 2001.

Applicants gratefully acknowledge the withdrawal of objections to the specification and claims, as well as rejections under 35 U.S.C. § 112, second paragraph.

Claims 13, 15-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78, and 85 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have replaced the term 'PYY agonist' throughout the claims with 'peptidyl PYY agonist', solely to expedite allowance of claims to this commercially important

embodiment. Such embodiments are discussed throughout the application, and particularly on pages 22 and 23. Applicants submit that the only proper concern under 35 U.S.C. § 112, second paragraph, is whether one of skill in the art would recognize the metes and bounds of the term 'peptidyl PYY agonist'. Applicants submit that this term, which provides both structural and functional definition, is sufficiently clear to comply with 35 U.S.C. § 112, second paragraph.

Applicants have also amended claim 28 to obviate the rejection of this claim as reciting improper Markush language. Although Applicants submit that this claim was proper in its previous form, Applicants have amended the claim without narrowing it in scope.

For the reasons given above, Applicants submit that the pending claims are in full compliance with 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 13-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78, and 85 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action alleges that the specification is enabled for PYY but not for the broader class of PYY therapeutics. Applicants submit, however, that as of the filing date, a number of other PYY analogs were available, as indicated by the references and abstracts provided previously as Exhibit **A**. Additionally, column 3 of U.S. Patent 5,574,010, incorporated by reference in the specification at the bottom of page 23, points out a number of other references relating to compounds that fall within the scope of the term 'PYY agonists'. Although the Office Action argues that the method of treating pancreatic tumors is not predictive to the method claimed in this application, the cited art fails to support the Office Action's allegations that a PYY agonist might retain some functions, such as tumor-fighting ability, without retaining others, such as the ability to modulate glucose metabolism. However, an enablement rejection must have a factual basis, and cannot rest solely on conjecture that the allegedly pleiotropic functions of PYY are separable, a conjecture that is unsupported by any experimental observation of record. Here, the Office Action fails to point to a single piece reference which

teaches a PYY agonist that lacks any function of PYY. Accordingly, Applicants assert that PYY agonists must be presumed to retain all functions of PYY in the absence of any contrary evidence.

Applicants direct the Examiner's attention to MPEP 2164.04. This section delineates the Examiner's burden "to establish a *reasonable* basis to question the enablement provided for the claimed invention." (emphasis added) Specifically, "it is incumbent upon the Patent Office, whenever a rejection on this basis, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Applicants point in particular to the requirement that the rejection be supported by evidence or sound logical reasoning. Applicants respectfully remind the Examiner that the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. If the Examiner is relying on art not made of record, Applicants respectfully request that such art be made of record so that it can be directly rebutted. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

Nevertheless, Applicants have amended the claims to recite that the PYY agonist is peptidyl. The art at the time of filing included a panoply of compounds that are 'peptidyl PYY agonists' as this term is used in the specification and pending claims, and Applicants have pointed to a number of such agonists in the documents already made of record. The specification on pages 22 and 23 describes techniques for synthesizing mutant, truncated, and other variant sequences of PYY which can be tested in the assays provided on pages 49-52. One of ordinary skill in the art could have identified any number of additional PYY agonists using only routine experimentation. Because PYY is a 36-amino acid sequence, the set of mutation and truncation

variants is substantially smaller than would be true of most proteins and enzymes. Moreover, Souli et al., previously made of record by Applicants, found that the fragment of amino acids 22-36 displayed potent antisecretory activities similar to full-length PYY. This observation was later confirmed by Balasubramanian et al., who found that an acetylated version of this fragment was even more potent than full-length PYY. Applicants respectfully remind the Examiner that "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01(a).

The Advisory Action states that "Litvak and Balasubramanian were published post-filing date of the instant application and cannot be considered." This statement, however, is contrary to the law. MPEP 2107.03, which permits the filing of data to rebut a rejection under 35 U.S.C. § 101, inherently supports this position, since such data need not have been known in the prior art nor have been provided in the application as filed. The Federal Circuit has endorsed this approach, reversing an examiner's rejection on utility *and enablement* grounds based on a declaration provided during prosecution demonstrating that the compounds possessed the antitumor activity alleged in the application. *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995).

Even the Utility Training Materials used in the Patent and Trademark Office follow this approach. Applicants direct the Examiner's attention to Example 11, page 61, in which Applicants respond to a utility rejection with a declaration supporting the asserted utility of one of the claimed inventions. The Materials state that "[t]he examiner should withdraw the rejection ... in light of this evidence." Although Applicants recognize that Faye et al. is not a declaration, evidence of this type is routinely used interchangeably with declarations under 37 C.F.R. § 132 to provide evidence in support of the enablement or utility of claimed subject matter. The case law and administrative documents discussed above merely demonstrate that the availability of such evidence before the filing date of an application is not necessary for its consideration and successful rebuttal of a utility rejection.

Most importantly, the Training Materials For Examining Patent Applications With Respect To ... Enablement specifically contemplate the presentation of post-filing evidence. Section V. Exemplary quotes include: "This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works." "An

applicant may argue that the FDA has approved clinical trials.... Applicant should be encouraged to provide *any evidence* to demonstrate that the disclosure enables the claimed invention, including evidence actually submitted to the FDA to obtain approval for clinical trials." (emphasis added) Obviously, such evidence would not have been available, no less published, prior to the filing of the application in question. Nevertheless, such evidence may be taken into account for its relevance to the *actual* enablement of the claims as of the filing date of the application. Again, Applicants rely on these post-filing date references not to show the existence of PYY agonists, but to show a) the correlation between *in vivo* and *in vitro* activities of PYY and PYY agonists, which would have been no different if tested prior to the filing date of the present application, and b) the actual functional attributes of PYY and PYY agonists as asserted in the specification and taught in art filed *prior* to the filing date of the present application. Consideration of these references for what they show *about the prior art and the application as filed* is urged.

The Advisory Action places considerable weight that no PYY agonist prior to the subject application had been taught to have the functions recited in the claims. From a logical standpoint, this amounts to a rejection of Applicants' invention as non-enabled on the basis that it is not rendered unpatentable by prior art. Clearly, the Framers of the Constitution, the drafters of the Patent Acts, and the Court of Appeals for the Federal Circuit disagree with this position. Applicants plainly asserted that PYY agonists generally, and peptidyl PYY agonists specifically, would function as PYY itself in the claimed methods in the application as filed. Applicants repeat that not a shred of evidence has been introduced which provides any logical or scientific basis to discount this contention. As noted above, a patent application is *presumed enabling*. Mere untested hypothesis is insufficient grounds for maintaining an enablement rejection, particularly in the face of evidence provided by Applicants that PYY agonists known at the time of filing were functionally equivalent to PYY itself in any of several respects.

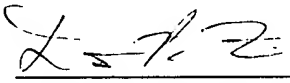
For all of the above reasons, which demonstrate that the present claims were enabled throughout their scope at the time of filing, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,



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